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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte RONALD J. PETTIS, JAMES A. DOWN, and NOEL G. HARVEY

Appeal 2010-006501
Application 09/606,909
Technology Center 3700

Before LINDA E. HORNER, STEVEN D.A. McCARTHY, and GAY ANN SPAHN, *Administrative Patent Judges*.

HORNER, *Administrative Patent Judge*.

DECISION ON APPEAL

STATEMENT OF THE CASE

Ronald J. Pettis et al. (Appellants) seek our review under 35 U.S.C. § 134 of the Examiner's decision rejecting claims 2-4, 10-13, 15, 16, and 29. Claims 17-24 and 32-39 are withdrawn from consideration and claims 1, 5-

9, 14, 25-28, 30, and 31 are canceled. We have jurisdiction under 35 U.S.C. § 6(b). We REVERSE.

THE INVENTION

Appellants' claimed invention relates to a method "for administration of substances into the skin." Spec. 1, ll. 8-9. Claim 29, reproduced below, is the sole independent claim on appeal and is representative of the subject matter on appeal.

> 29. A method for administration of insulin to a human subject, comprising delivering the insulin through the lumen of a hollow needle into an intradermal compartment of the human subject's skin, which method comprises
>
> (a) inserting the needle into the subject's skin so that the needle penetrates the intradermal compartment, and the needle's outlet depth and exposed height of the outlet are located within the intradermal compartment, wherein the outlet has an exposed height of about 0 to 1 mm; and
>
> (b) delivering the insulin through the lumen of the needle with the application of pressure in an amount effective to control the rate of delivery of the insulin, so that the insulin is delivered through the lumen of the needle into the intradermal compartment and distributed systemically exhibiting a higher maximum plasma concentration and a higher bioavailability as compared to subcutaneous delivery.

THE EVIDENCE

The Examiner relies upon the following evidence:

Gross '375	US 5,807,375	Sep. 15, 1998
Gross '991	US 5,848,991	Dec. 15, 1998
Srivastava	US 6,007,821	Dec. 28, 1999
D'Antonio	US 6,056,716	May 2, 2000
Prausnitz	US 6,611,707 B1	Aug. 26, 2003

E. Autret et al., *Comparaison des concentrations plasmatiques et de la tolérance d'une dose unique de calcitonine humaine administrée par voie intradermique et sous-cutanée*, 46 Therapie, 5-8 (1991) ("Autret").

Navneet Puri et al., *An investigation of the intradermal route as an effective means of immunization for microparticulate vaccine delivery systems*, 18 Vaccine, 2600-12 (2000) ("Puri").

The Merck Manual of Diagnosis and Therapy, 2556-71 (Merck Research Labs.) (17th Ed., Mark H. Beers, M.D. et al. eds., 1999) ("Merck Manual").

Appellants rely upon the following additional evidence:

Hubbard US 5,505,694 Apr. 9, 1996

Gregory M. Glenn et al., *Advances in vaccine delivery: transcutaneous immunisation*, 8 Exp. Opin. Invest. Drugs, 797-805 (1999) ("Glenn").

Declaration of Dr. Gerald B. Kasting Under 37 C.F.R. § 1.132, filed October 7, 2005 ("Kasting Decl.").

Declaration of Dr. Ronald J. Pettis Under 37 C.F.R. § 1.132, dated January 6, 2005 ("First Pettis Decl.").

Second Declaration of Dr. Ronald J. Pettis Under 37 C.F.R. § 1.132, filed October 7, 2005 ("Second Pettis Decl.").

Third Declaration of Dr. Ronald J. Pettis Under 37 C.F.R. § 1.132, filed June 18, 2007 ("Third Pettis Decl.").

Amendment Under 37 C.F.R. § 1.111, dated October 7, 2005.

Amendment and Response Under 37 C.F.R. § 1.111, dated June 18, 2007.

Application 09/606,909 as originally filed on June 29, 2000.

THE REJECTION[1]

Appellants seek review of the rejection of claims 2-4, 10-13, 15, 16, and 29 under 35 U.S.C. § 103(a) as being unpatentable over Gross '991 or Gross '375 in view of Prausnitz, Autret, Puri, D'Antonio, Srivastava, and Merck Manual.

ISSUE

The Examiner determined that both Gross '991 and Gross '375 disclose a method of delivering drugs, including insulin, intradermally using a needle that extends into the intradermal layer, and, as modified by the teaching of Prausnitz, would result in a needle outlet having an exposed height of 0 – 1 mm. Ans. 4. The Examiner acknowledged that Gross '991 and Gross '375, as modified by Prausnitz, are silent with respect to the pharmacokinetic profile of the intradermal delivered drugs. *Id.* The Examiner determined that it would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Autret, Puri, D'Antonio, or Srivastava in the modified drug delivery method of Gross '991 or Gross '375 "to deliver effective drug treatments at particular pressures and flow rates to achieve higher C_{max} and bioavailability with

[1] Appellants also sought review of provisional, non-statutory, obviousness-type double patenting rejections of claims 2-4, 10-13, 15, 16, and 29 over certain claims of Applications 10/028,988 and 10/028,989. App. Br. 8. Since the filing of the Appeal Brief, Applications 10/028,988 and 10/028,989 have been abandoned, thereby rendering the above-referenced double patenting rejections moot. As such, we do not reach these rejections.

intradermal injection as compared to subcutaneous injection in order to effectively treat patients using lower dosages, thereby saving drug costs and inventories." Ans. 6.

Appellants argue that the Examiner's reliance on Puri, D'Antonio, and Srivastava is misplaced because these references relate to the administration of vaccines, which are not distributed systemically in the bloodstream, and as a result do not display pharmacokinetic profiles. App. Br. 16-17. Appellants also argue that the Examiner's reliance on Autret is misplaced because while Autret describes a drug delivery method and the pharmacokinetic profile achieved by that method, Autret does not provide a reason to modify Gross '991 or Gross '375 in the manner claimed because Autret teaches that the bioavailability achieved using Autret's approach is no different from that obtained by the subcutaneous injection. App. Br. 18-20.

The issue presented by this appeal is whether the Examiner articulated adequate reasoning based on rational underpinnings to explain why a person of ordinary skill in the art would have been led to modify the method of Gross '991 or Gross '375 to deliver the insulin through the lumen of the needle with the application of pressure in an amount effective to control the rate of delivery of the insulin so as to result in the pharmacokinetic profile as called for in claim 29.

ANALYSIS

Puri, D'Antonio, and Srivastava each relate to the administration of vaccines intradermally versus subcutaneously. Puri, Abstr. and p. 2609 ("The enhancement in antibody production upon id administration was

explained on the basis of (i) an increased surface area of microspheres and a lower number of microspheres per injection site, and (ii) an increased probability of interaction with the immune cells of the skin"); D'Antonio, col. 29, ll. 23-26 (describing that proper use of its injector to administer an intradermal vaccine will spread the injectant over a much wider radius than prior art needles and syringes which will "provide an increasingly rapid and effective pick-up by the immune system"); and Srivastava, col. 6, ll. 10-12, col. 19, l. 60 – col. 20, l. 25, and col. 24, ll. 34-36 (describing using heat shock protein as an adjuvant that modulates the immune response and "is mediated through the endogenous, local, cellular response instead of systemically"). Neither Puri, D'Antonio, nor Srivastava teaches what difference, if any, intradermal administration of drugs, such as insulin or other hormone drugs that are delivered to the systemic circulation, has on the maximum plasma concentration (C_{max}) and bioavailability as compared to subcutaneous delivery. As such, the Examiner's reasoning explaining why one of ordinary skill in the art would have been led to modify the drug delivery methods of Gross '991 or Gross '375 to achieve the claimed pharmacokinetic profile in light of Puri, D'Antonio, or Srivastava is not based on rational underpinnings.

The Examiner found that "Autret discloses intradermal injection of a hormone resulting in a pharmacokinetic profile similar to subcutaneous delivery, but with a higher plasma level and bioavailability as assessed by C_{max} and T_{max} (Figure 1)." Ans. 5. *See also* Ans. 10 ("it is the Examiner's position that the disclosure of Autret of higher bioavailability (as calculated

by C_{max} and T_{max}) of drug when administered intradermally as compared to subcutaneous administration teaches the claimed limitation.").

As discussed *infra*, Autret teaches that intradermic administration of the drug that was the subject of the study did not achieve improved bioavailability as compared to subcutaneous administration. In light of this teaching, we find that the Examiner's articulated reason to modify Gross '991 or Gross '375 with Autret is not based on rational underpinnings. Autret relates to a study to determine whether administration of synthetic human calcitonin Cibacalcine® via an intradermic route by mesotherapic technique exhibits a more rapid and superior resorption than via a subcutaneous route. Autret, p. E5.[2] The object of the study was to compare the plasmatic concentrations of calcitonin after administration of the drug via the intradermic route and via the subcutaneous route. *Id.* Autret discloses that "[t]he evaluation concerned the maximum concentration (C_{max}), the time to obtain the C_{max} (T_{max}), the area under the curve of plasmatic concentrations as a function of the time (AUC)." *Id.* at p. E6. Autret presented the results in a table which looked at the area under the curve of the plasmatic concentrations of calcitonin as a function of time for the intradermic route and for the subcutaneous route. Autret, p. E9 (Table I). The Table reported "BD: relative bioavailability of the ID route relative to the SC route." *Id.* Autret determined that "[t]he plasmatic concentrations at

[2] Citations to Autret refer to the English language translation provided as Exhibit E in the Evidence Appendix to Appellants' Appeal Brief on pages E5-E14.

the different times are not significantly different with the routes of administration (fig. 1)" and that "[t]he AUC obtained with the 2 routes of administration calculated between TO and successively H24, H8, H4 are not different (*table I*)." Autret, p. E10. Autret concluded that "[t]here are no controlled studies that permit the efficacy advanced by the practitioners of mesotherapy to be confirmed. These facts speak against a more rapid or greater resorption put forward to justify mesotherapy." Autret, p. E14. *See also* Kasting Decl., at para. 19 ("The pharmacokinetic profile disclosed in Autret (*see*, Autret, Fig. 1) is not improved over subcutaneous delivery – in fact, the profiles for the two routes of delivery are nearly identical."). Based on these teachings of Autret, the Examiner's reasoning that one of ordinary skill in the art would have been led to modify the drug delivery method of Gross '991 or Gross '375 based on the teachings of Autret to deliver the drug treatments at particular pressures and flow rates to achieve higher C_{max} and bioavailability with intradermal injection as compared to subcutaneous injection is without rational underpinning.

CONCLUSION

The Examiner did not articulate adequate reasoning based on rational underpinnings to explain why a person of ordinary skill in the art would have been led to modify the method of Gross '991 or Gross '375 to deliver the insulin through the lumen of the needle with the application of pressure in an amount effective to control the rate of delivery of the insulin so as to result in the pharmacokinetic profile as called for in claim 29.

DECISION

We REVERSE the decision of the Examiner to reject claims 2-4, 10-13, 15, 16, and 29 under 35 U.S.C. § 103(a).

REVERSED

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